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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34133 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US00/30892

(22) International Filing Date:
9 November 2000 (09.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/164,705 11 November 1999 (11.11.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/34133 A2

(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: The therapeutic combinations of leukotriene (LTB4) inhibitors and anti-cancer agents are disclosed. A method of treating cancer using leukotriene (LTB4) inhibitors in conjunction with anti-cancer agents is also disclosed.

ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from United States Provisional Patent Application No. 60/164,705 filed 11 November 1999; the entire disclosure of which is incorporated by reference.

FIELD OF THE INVENTION

This invention relates to a method of treating cancer with anti-cancer agents. More specifically, it relates to the use of anti-cancer agents, in conjunction with leukotriene (LTB_4) antagonists that enhance the effectiveness of the anti-cancer agents.

BACKGROUND OF THE INVENTION

Leukotriene B_4 (LTB_4) is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, asthma, inflammatory bone diseases and other inflammatory states

characterized by the infiltration and activation of polymorphonuclear leukocytes and other proinflammatory cells. Thus activated, the polymorphonuclear leukocytes liberate tissue-degrading enzymes and reactive chemicals causing the inflammation. US Patent 5,462,954 discloses phenylphenol leukotriene antagonists which are useful in the treatment of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, asthma, inflammatory bone diseases and other inflammatory states characterized by the infiltration and activation of polymorphonuclear leukocytes and other pro inflammatory cells. US Patent 5,910,505 discloses that certain phenylphenol leukotriene B_4 (LTB_4) antagonists are useful as agents for the treatment of oral squamous cell carcinoma. US Patent 5,543,428 discloses a group of phenylphenol leukotriene antagonists which have the property of reversing multi-drug resistance in tumor cells. The use of the leukotriene antagonist will reverse the drug resistance of resistant tumor cells to vinblastine, vincristine, vindesine, navelbine, daunorubicin, doxorubicin, mitroxantrone, etoposide, teniposide, mitomycin-C, actinomycin-D, taxol, topotecan, mithramycin, colchicine, puromycin, podophylotoxin, emetine, gramicidin-D, and valinomycin

BRIEF SUMMARY OF THE INVENTION

This invention provides compositions and methods useful for treating cancers, which are not multi-drug resistant. The compositions of the present invention include anti-cancer agents in combination with leukotriene (LTB_4) antagonists.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions:

The term, "Active Ingredient" refers both to certain anti-cancer agents described below and also certain leukotriene B4 antagonist compounds, also described below, and the salts, solvates, and prodrugs of such compounds.

The term, "LTB_4 antagonist" means any agent that inhibits the actions of LTB_4 or its synthesis, or increases its biochemical breakdown.

The terms, "mammal" and "mammalian" include human.

The term "therapeutically effective interval" is a period of time beginning when one of either (a) the 2', 2'-difluoronuceoside anti-cancer agent or (b) the LTB_4 antagonist is administered to a mammal and ending at the limit of the anti-cancer beneficial effect in treating cancer of (a) or (b). Typically, the anti-cancer agents and the leukotriene (LTB_4) antagonist are administered within 24 hours of each other, more preferably within 4 hours and most preferably within 1 hour.

The phrase "therapeutically effective combination", used in the practice of this invention, means administration of both (a) the anti-cancer agent(s) and (b) the LTB_4 antagonist, either simultaneously or separately.

Suprisingly, we have found that the combination of certain anti-cancer agents with leukotriene (LTB_4)

antagonists is highly effective in treating cancers that are not multi-drug resistant.

The types of cancers which may be treated with the compositions of the present invention include: Breast Carcinoma, Bladder Carcinoma, Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeoma, Neurologic Carcinoma, Brain Cancer, Non-Small Cell Lung Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Soft Tissue Sarcoma, Pediatric Malignancies and the like.

The anti cancer agents which may be used include:

ALKYLATING AGENTS: Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide;

ANTIBIOTICS: Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin;

ANTIMETABOLITES: Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine, Capecitabine;

BIOLOGICALS: Aldesleukin, Interferon Alfa-2A, Interleukin2, Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin;

HORMONAL AGENTS: Aminoglutethimide, Anastrozole, Flutamide, Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen;

NITROGEN MUSTARD DERIVATIVES: Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa;

PLANT ALKALOIDS: Docetaxel, Etoposide, Irinotecan HCL, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine;

OTHERS: Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, Procarbazine, and the like.

The anti-cancer agents may be used alone or in combinations of one or more anti-cancer agents. When used in combination, the anti-cancer agents may be administered at the same time, sequentially or in more complicated regimens where the agents may be administered alternately. Such combinations and dosing regimens are well known to those skilled in the art. The anti-cancer agents may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered transdermally and may be formulated as sustained relief dosage forms and the like.

The compositions of the present invention are a combination of therapeutically effective amounts of the leukotriene (LTB_4) antagonists, noted above, and a therapeutically effective amount of an anti-cancer agent. The composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered transdermally and may be formulated as sustained relief dosage forms and the like.

In another embodiment, the invention relates to a method of treating a patient suffering from a non-multi-drug resistant cancerous condition which comprises the separate administration of a therapeutically effective amount of the leukotriene (LTB_4) antagonists, and the anti-cancer agent. When administered separately, the leukotriene (LTB_4) antagonists, and the anti-cancer agent may be administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. Therapeutically effective interval is a period of time beginning when one of either (a) the leukotriene (LTB_4) antagonists or (b) the anti-cancer agent is administered to a human and ending at the limit of the beneficial effect in the treatment of cancer of the combination of (a) and (b).

The methods of administration of the leukotriene LTB_4 antagonist and the anti-cancer agent may vary. Thus, one agent may be administered orally, while the other is administered intravenously. It is possible that one of the products may be administered as a continuous

infusion while the other is provided in discreet dosage forms. It is particularly important that the anti-cancer drug be given in the manner known to optimize its performance.

Leukotriene B_4 receptor antagonists suitable for (i) pharmaceutical compositions of the invention, and (ii) practicing the cancer treatment and prevention methods of the invention are as follows: calcitriol, ontazolast, Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, LeoDenmark ETH-615, Ono ONO-4057, Terumo TMK-688, Boehringer Ingleheim BI-RM-270, Ono ONO LB457, Pfizer 105696, Perdue Frederick PF 10042, Rhone-Poulenc Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline Beecham SB-201993, SmithKline Beecham SB-209247, Searle SC-53228, Sumitomo SM 15178, American Home Products WAY 121006, Bayer Bay-o-8276, Warner Lambert CI-987, Warner Lambert CI-987BPC-15, MacroNex MNX-160, Merck and Co. MK-591, Merck and Co. MK-886, Ono ONO-LB-448, Purdue Frederick PF-5901, Roche Ro 25-3562, Rhone-Poulenc Rorer RG 14893, Rhone-Poulenc Rorer RP66364, Rhone-Poulenc Rorer RP69698, Shionogi S-2474, Searle SC-50605, Searle SC-41930, Searle SC-50505, Searle SC-51146, Searle SC-52798, SmithKline Beecham SK&F-104493, Leo Denmark SR-2566, Tanabe T-757, and Teijin TEI-1338, Lilly LY213024, Lilly LY264086, Lilly LY255283, Lilly LY210073, Lilly LY247833, and Lilly LY282201, 2-[3-[3-(4-acetyl-2-ethyl-5 hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441).

The LTB_4 inhibitors described above (and additional LTB_4 inhibitors) are further identified by the chemical names and sources set out below (compounds (a.) through (vv.)) below.

Leukotriene B_4 inhibitors (and the pharmaceutically acceptable acid, salt, solvate, or ester derivatives thereof) suitable for (i) pharmaceutical compositions of the invention, and (ii) practicing the cancer treatment and prevention methods of the invention are as follows:

a.) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441)

b.) Roche Ro 21-5535(calcitriol;(1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3; calcijex; Rocaltrol; soltriol; topitriol; CAS Registry Number 32222-06-3)

c.) Parke-Davis CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5)

d.) Pfizer CP-195543 (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid; CAS Registry Number 204981-48-6)

e.) Wyeth-Ayerst WAY-121006 (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid; CAS Registry Number 136326-31-3)

f.) Bayer Bay-x-1005 ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid; CAS Registry Number 128253-31-6)

g.) Ciba-Geigy CGS-25019C (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-Benzamide; moxilubant; CAS Registry Number 147398-01-4)

h.) Nattermann & Cie GmbH ebselen (3 2-phenyl-1,2-Benzisoselenazol-3(2H)-one; CAS Registry Number 60940-34)

i.) Leo Denmark ETH-615 (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid; CAS Registry Number 133430-69-0)

j.) Ono ONO-4057 (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid; CAS Registry Number 134578-96-4)

k.) Terumo TMK-688 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid; CAS Registry Number 110501-66-1)

l.) Boehringer Ingleheim BIRM-270 ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast; CAS Registry Number 147432-77-7)

m.) Ono ONO-LB457 (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid; CAS Registry Number 134578-96-4)

n.) Pfizer 105696 (1-[(3S,4R)-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-cyclopentanecarboxylic acid; CAS Registry Number 158081-99-3)

o.) Perdue Frederick PF 10042 (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl] pyrroline; CAS Registry Number 135893-33-3)

p.) Rhone-Poulenc Rorer RP 66153 (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid; CAS Registry Number 142422-795)

q.) SmithKline Beecham SB-201146 ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-

methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid; CAS Registry Number 180208-37-1)

r.) SmithKline Beecham SB-201993 ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid; CAS Registry Number 150399-22-7)

s.) SmithKline Beecham SB-209247 ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant; CAS Registry Number 154413-61-3)

t.) Searle SC-53228 (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 153633-01-3)

u.) Sumitomo SM 15178 (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine; CAS Registry Number 104227-11-4)

v.) Bayer Bay 0-8276 (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide; BAY 08276 CAS Registry Number 85259-71-8)

w.) Warner Lambert CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5)

x.) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y.) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z.) Merck and Co. MK-886 (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7)

aa.) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb.) Purdue Frederick PF-5901 (α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol; CAS Registry Number 101910-24-1)

cc.) Roche Ro 25-3562 (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane; AI 3-70356; Roller's synthetic juvenile hormone; CAS Registry Number 38896-81-0)

dd.) Rhone-Poulenc Rorer RG 14893 (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid; CAS Registry Number 141835-49-6)

ee.) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff.) Rhone-Poulenc Rorer RP69698 (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine; CAS Registry Number 141748-00-7)

gg.) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh.) Searle SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 138828-39-4)

ii.) Searle SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 120072-59-5)

jj.) Searle SC-50505 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-

dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry 138828-39-4)

kk.) Searle SC-51146 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 141059-52-1)

ll.) Searle SC-52798 (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 152246-97-4)

mm.) SmithKline Beecham SK&F-104493 (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole; CAS Registry Number 111908-95-3)

nn.) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo.) Tanabe T-757 (CAS Registry 187112-56-7)

pp.) Teijin TEI-1338 [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester; CAS Registry Number 119261-58-4)

qq.) Lilly LY213024 (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid; CAS Registry Number 117423-95-7)

rr.) Lilly LY264086 (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid; CAS Registry Number 135199-82-5)

ss.) Lilly LY255283 (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356; CAS Registry Number 117690-79-6)

tt.) Lilly LY247833 (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol)

uu.) Lilly LY282201 (3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid),

vv.) Lilly LY210073 (CAS Registry Number 186912-79-8).

The above LTB_4 receptor antagonists are identified by company identifiers and code numbers which are readily converted to names of specific chemical compounds by using well-known databases of chemical literature and medicinal chemistry such as; "Chemical Abstracts Database" (product of Chemical Abstracts Co.) and "The Investigational Drug Database" (product of Current Drugs Ltd.).

In many cases the above specific LTB_4 receptor antagonists (identified by company identifiers and code numbers) are described as species in patents of the above identified companies. These patents most often describe a genus of compounds having utility as LTB_4 receptor antagonists, where the above identified species are single compounds within the genus taught or claimed by these patents. Therefore, all the compounds within such taught or claimed patent genera are also considered to be within the scope of the compounds considered useful in the compositions and methods of use of this invention.

The salt derivatives of the LTB_4 antagonist, anti-cancer agent of the composition and method of the invention are pharmaceutically acceptable salts, that include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid (e.g., carboxylic acid, sulfonic acid, phosphonic acid) in solution with a base or by exposing the acid to an acidic cation charged ion exchange resin. For example, a carboxylic acidic group (a preferred acidic group) may

form a salt by reaction with appropriate bases (e.g., NaOH, KOH) or sodium or potassium charged acidic ion-exchange resins to yield the corresponding sodium and potassium salt.

Certain compounds of the compositions or methods of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis and trans isomeric forms of the compounds. The R and S isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis and trans isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives

of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds used in the composition and method of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound used in the composition or method of the invention (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound used in the composition or method of the invention (in a medium such as dimethylformamide) with 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

In one embodiment the compositions of the present invention are a combination of therapeutically effective amounts of the leukotriene (LTB_4) antagonists, noted above, and a therapeutically effective amount of an anti-cancer agent or anti-cancer agents. The composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered transdermally and maybe formulated as sustained relief dosage forms and the like.

In another embodiment, the anti-cancer agents are formulated independently of the leukotriene (LTB_4) antagonists and are administered separately. The anti-cancer agents may be formulated with common excipients, diluents or carriers and administered by intravenous infusion. On the other hand, the anti-cancer agents may be formulated into liquids suitable for oral administration. Anti-cancer agents may also be compressed into tablets and administered orally. If the anti-cancer agents and the leukotrienes are administered separately, the anti-cancer agents may be administered before, after or during the administration of the leukotriene (LTB_4) antagonists. If the anti-cancer agents are administered separately from the leukotrienes

(LTB_4) antagonists, they must be administered within a therapeutically effective interval.

The method of treating a human patient according to the present invention includes both the administration of the combination of leukotriene (LTB_4) antagonists and an anti-cancer agent as well as the separate administration of the leukotriene (LTB_4) antagonists and the anti-cancer agent. When administered separately, the leukotriene (LTB_4) antagonists are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I or Formula II. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the

condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations useful for separate administration of the leukotriene (LTB_4) antagonists will normally consist of at least one compound selected from the compounds of Formula I and Formula II mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered

ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, injectable solutions, creams and ointments. Especially preferred are formulations for inhalation application, such as an aerosol, and for oral ingestion.

The following formulation examples may employ as active compounds any of the leukotriene (LTB_4) antagonists noted above. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

The leukotriene (LTB_4) antagonists are generally administered prior, during and after the anti-cancer agent or agents are administered. If the leukotriene (LTB_4) antagonists are administered before or after the anti-cancer agent or agents, they should be administered within a therapeutically effective interval.

Pharmaceutical Compositions of the Invention

The pharmaceutical composition of the invention comprises as essential ingredients:

(a) an LTB_4 antagonist, and

(b) an anti-cancer agent.

When the pharmaceutical composition of the invention is prepared in injectable form it is a composition comprising as ingredients:

(a) an LTB_4 antagonist,

(b) an anti-cancer agent, and

(c) an injectable liquid carrier.

Pharmaceutically acceptable carriers are those well known in the medical arts, such as sterile water, sterile water containing saline, and sterile water containing sugars and/or saline.

a. Ratio and Amount of Ingredients in the Composition of the Invention

The essential ingredients (a) an LTB_4 antagonist and (b) anti-cancer compound are present in the formulation in such proportion that a dose of the formulation provides a pharmaceutically effective amount of each ingredient to the patient being treated. Typically, the weight ratio of LTB4 antagonist to anti-cancer agent 1:100 to 100 to 1, preferable from 10:1 to 1:10 and most preferable from 1:4 to 4:1.

We Claim:

1. A composition of matter comprising a therapeutically effective amount of a leukotriene (LTB_4) antagonist and one or more anti-cancer agents.

2. The composition according to claim 1 wherein the leukotriene (LTB_4) antagonist is selected from the group consisting of the following:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid;

b) (1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3;

c) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

d) (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid;

e) (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid;

f) ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid;

g) (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-Benzamide;

h) (3 2-phenyl-1,2-Benzisoselenazol-3(2H)-one;

i) (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid;

j) (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

k) 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid;

l) ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast;

m) (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

n) (1-[(3S,4R0-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-cyclopentanecarboxylic acid;

o) (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl] pyrroline;

p) (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid;

q) ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid;

r) ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid;

s) ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant;

t) (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid;

u) (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine;

v) (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide;

w) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z) (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536;

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) (α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol;

cc) (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane;

dd) (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid;

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff) (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine;

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

ii) (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

jj) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

kk) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid;

ll) (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

mm) (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole;

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo) Tanabe T-757 (CAS Registry 187112-56-7)

pp) [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester;

qq) (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid;

rr) (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid;

ss) (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356;

tt) (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol); and

(3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid);

and, the pharmaceutically acceptable acid, salt, solvate, or ester derivatives thereof.

3. The composition of claim 1 wherein the anti-cancer agent is selected from the group consisting of Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin, Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine; Capecitabine, Aldesleukin, Interferon Alfa-2A, Interleukin2, Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin, Aminoglutethimide, Anastrozole, Flutamide, Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen, Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa, Docetaxel, Etoposide, Irinotecan HCl, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, and Procarbazine.

4. The composition of claim 2 wherein the anti-cancer agent is selected from the group consisting of Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin, Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine; Capecitabine, Aldesleukin, Interferon Alfa-2A, Interleukin-2, Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin, Aminoglutethimide, Anastrozole, Flutamide, Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen, Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa, Docetaxel, Etoposide, Irinotecan HCl, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, and Procarbazine.

5. The use in the manufacture of a medicament for the treatment of cancer in a mammal of a therapeutically effective amount of a leukotriene (LTB_4) antagonist in combination with a therapeutically effective amount of one or more anti-cancer agents.

6. The use according to claim 5 wherein the leukotriene (LTB_4) antagonist is selected from the group consisting of the following:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid;

b) (1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3;

c) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

d) (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid;

e) (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid;

f) ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid;

g) (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-Benzamide;

h) (3 2-phenyl-1,2-Benzisoselenazol-3(2H)-one;

i) (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid;

j) (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

k) 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid;

l) ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast;

m) (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

n) (1-[(3S,4R0-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-cyclopentanecarboxylic acid;

o) (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl] pyrroline;

p) (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid;

q) ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid;

r) ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid;

s) ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant;

t) (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid;

u) (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine;

v) (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide;

w) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z) (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536;

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) (α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol;

cc) (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane;

dd) (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid;

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff) (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine;

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

ii) (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

jj) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

kk) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid;

ll) (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

mm) (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole;

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo) Tanabe T-757 (CAS Registry 187112-56-7)

pp) [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester;

qq) (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid;

rr) (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid;

ss) (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356;

tt) (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol); and

(3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid);

and, the pharmaceutically acceptable acid, salt, solvate, or ester derivatives thereof.

7. The use of claim 5 wherein the anti-cancer agent is selected from the group consisting of Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin, Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine; Capecitabine, Aldesleukin, Interferon Alfa-2A, Interleukin-2, Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin, Aminoglutethimide, Anastrozole, Flutamide,

Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen, Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa, Docetaxel, Etoposide, Irinotecan HCL, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, and Procarbazine.

8. The composition of claim 6 wherein the anti-cancer agent is selected from the group consisting of Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin, Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine; Capecitabine, Aldesleukin, Interferon Alfa-2A, Interleukin-2, Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin, Aminoglutethimide, Anastrozole, Flutamide, Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen, Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa, Docetaxel, Etoposide, Irinotecan HCL, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, and Procarbazine.

9. A method of treating cancer in a human patient by administering to said patient a composition comprising a therapeutically effective amount of a leukotriene (LTB_4) antagonist and one or more anti-cancer agents.

10. The method of claim 9 wherein the leukotriene (LTB_4) antagonist is selected from the group consisting of the following:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid;

b) (1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3;

c) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

d) (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid;

e) (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid;

f) ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid;

g) (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl)-Benzamide;

h) (3 2-phenyl-1,2-Benzisoselenazol-3(2H)-one;

i) (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid;

j) (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

k) 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid;

l) ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast;

m) (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

n) (1-[(3S,4RO-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-cyclopentanecarboxylic acid;

o) (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl] pyrroline;

p) (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid;

q) ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid;

r) ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid;

s) ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant;

t) (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-Benzopyran-2-propanoic acid;

u) (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine;

v) (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide;

w) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z) (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536;

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) (α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol;

cc) (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyloxirane;

dd) (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid;

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff) (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine;

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

ii) (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

jj) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

kk) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid;

35

ll) (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

mm) (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole;

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo) Tanabe T-757 (CAS Registry 187112-56-7)

pp) [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester;

qq) (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid;

rr) (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid;

ss) (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356;

tt) (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol); and

(3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid);

and, the pharmaceutically acceptable acid, salt, solvate, or ester derivatives thereof.

11. The method of claim 9 wherein the anti-cancer agent is selected from the group consisting of Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin, Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine; Capecitabine, Aldesleukin, Interferon Alfa-2A, Interleukin-2, Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin, Aminoglutethimide, Anastrozole, Flutamide, Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen, Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa, Docetaxel, Etoposide, Irinotecan HCL, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, and Procarbazine.

12. The method of claim 10 wherein the anti-cancer agent is selected from the group consisting of Busulfan, Carboplatin, Carmustine, Cisplatin, Cyclophosphamide, Dacarbazine, Ifosfamide, Lomustine, Streptozocin, Oxaliplatin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, Mitomycin-C, Plicamycin, Cryptophycin, Cytarabine, Floxuridine, Fludarabine, 5-Fluorouracil, Hydroxyurea, 6-Mercaptopurine, Methotrexate, Thioguanine; Capecitabine, Aldesleukin, Interferon Alfa-2A, Interleukin-2,

Interleukin-12 (recombinant), Interferon Alfa-2B (recombinant), Interferon Alfa-n3, Interferon Gamma-1B, Herceptin, Aminoglutethimide, Anastrozole, Flutamide, Goserelin, Leuprolide, Megestrol, Mitotane, Tamoxifen, Chlorambucil, Estramustine, Mechlorethamine, Melphalan, Thiotepa, Docetaxel, Etoposide, Irinotecan HCL, Paclitaxel, Teniposide, Topotecan, Vinblastine, Vincristine, Vinorelbine, Altretamine, Amifostine Asparaginase-*Escherichia coli* strain, BCG Live (Intravesical), Cladribine, Leucovorin, Levamisole, Mitoxantrone, Pegaspargase, Pentostatin, and Procarbazine.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 May 2001 (17.05.2001)

PCT

(10) International Publication Number
WO 01/34133 A3

(51) International Patent Classification[7]: A61K 45/06, A61P 35/00

(21) International Application Number: PCT/US00/30892

(22) International Filing Date:
9 November 2000 (09.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/164,705 11 November 1999 (11.11.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
14 February 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/34133 A3

(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: The therapeutic combinations of leukotriene (LTB4) inhibitors and anti-cancer agents are disclosed. A method of treating cancer using leukotriene (LTB4) inhibitors in conjunction with anti-cancer agents is also disclosed.

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/US 00/30892

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 47890 A (G.D. SEARLE) 29 October 1998 (1998-10-29) claim 1 page 7, line 18-21 page 8, line 24 -page 13, line 25 page 14, line 17-34	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2001	14/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-12 relate to an extremely large number of possible compositions/uses/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions/uses/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out completely for the first LTB4 antagonist compound and for the first anti-cancer compound cited in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten nal Application No
PCT/US 00/30892

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